REMARKS

Claims 1-2, 4-35 and 37-41 are pending. Claims 3 and 36 are cancelled. Claims 2, 8, 14 and 32 are withdrawn. Thus, Claims 1, 4-7, 9-13, 15-31, 33-35 and 37-41 are currently under examination.

Rejection Under 35 U.S.C. §103(a) Over PACETTI in View of SHEU

The Examiner has rejected Claims 1, 4-7, 9-10, 20-30, 33-34 and 37-41 under 35 §U.S.C. 103(a) on the basis of Pacetti et al (US Patent 6,663,662) ("PACETTI") in view of Sheu et al (US Patent 5,837,377) ("SHEU"). This rejection is respectfully traversed.

It is believed that the Examiner has not met his burden of establishing a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claimed features. Also, according to the MPEP in a discussion under Section 2141:

> "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). (emphasis added)

Thus, in order to combine references, there must be some logical reason to do so and some reason that the technologies are, in fact, combinable.

In the first instance it is important to note that the focus of each of PACETTI and SHEU is very different. PACETTI focuses on controlling the rate of drug release from a medical device such as a stent by using a diffusion barrier. SHEU does not teach or suggest the release of any drug from a polyelectrolyte coating and instead focuses on improving the wettability of polymers, especially those to be used in aqueous

environments, for example, with contact lenses. In general and specifically, one skilled in the art would not look to SHEU to find suitable coatings to be used in PACETTI.

PACETTI discloses a metallic stent carrying a therapeutic or bioactive substance and having a diffusion barrier to reduce the rate at which the therapeutic or bioactive substance is released and, optionally, a plurality of cavities or micro-pores formed in the body for releasably containing the active ingredient. The diffusion barrier comprises a polymeric material impregnated with particles.

In contrast to PACETTI the present invention requires:

> (b) a multilayer coating region comprising multiple polyelectrolyte layers deposited over said surface wherein each polyelectrolyte layer has a net charge opposite in sign from the adjacent layers; and (c) a therapeutic agent disposed within the depressions beneath said multilayer coating region (excerpt from Claim 1) (emphasis added)

The Examiner agrees that PACETTI neither teaches nor suggests polyelectrolyte layers covering a stent. (Office Action, page 4). As a corollary to this point, **PACETTI also does not disclose a therapeutic agent disposed within the depressions beneath said multilayer coating region comprising polyelectrolyte layers.** The Examiner then looks to SHEU in order to fill in these deficiencies.

SHEU focuses on improving the wettability of polymers, especially those to be used in aqueous environments, for example, with contact lenses. SHEU teaches hydrophilic articles with a durable hydrophilic coating wherein the article comprises a substrate, an ionic polymeric layer on the substrate and a disordered polyelectrolyte coating which is ionically bonded to the ionic polymer layer (see col.1, lines 20-24). It is important to note that SHEU does not teach or suggest:

1) the release of any therapeutic agent from the polyelectrolyte coating; or

2) controlling the rate of release of a therapeutic agent by using a diffusion barrier of the type described in PACETTI.

Thus, both SHEU and PACETTI alone or together fail to teach or suggest **a therapeutic agent disposed within the depressions beneath said multilayer coating region comprising polyelectrolyte layers.**

Moreover, PACETTI is not even combinable with SHEU for a number of reasons:

First, the Examiner has ignored the effect of the presence of an active ingredient (taught in PACETTI) on the articles of SHEU and the effect of the hydrophilicity requirement of SHEU. In particular, PACETTI notes:

> The presence of an active ingredient in a polymeric matrix typically interferes with the ability of the matrix to adhere effectively to the surface of the device. An increase in the quantity of the active ingredient reduces the effectiveness of the adhesion. High drug loadings of, for example, 10-40% by weight in the coating significantly hinder the retention of the coating on the surface of the device. The primer layer serves as a functionally useful intermediary layer between the surface of the device and an active ingredient-containing or reservoir coating. The primer layer provides for an adhesive tie between the reservoir coating and the device--which, in effect, would also allow for the quantity of the active ingredient in the reservoir coating to be increased without compromising the ability of the reservoir coating to be effectively contained on the device during delivery and, if applicable, expansion of the device. (col.7, lines 58-64)

The use of an active ingredient in PACETTI would impact the hydrophilicity of SHEU and the adherence of a layer to the surface as taught by PACETTI, and SHEU's requirement that the articles have durable hydrophilicity will impact the activity of a device and the coatings used, such as on the stent described in PACETTI that contains a therapeutic agent.

Second, PACETTI does not use a surface treatment. PACETTI clearly states that no surface treatment is needed to retain the coating for its devices (col.16, lines 30-31). The device in PACETTI may be coated using conventional methods such as spraying or immersing the device in order to coat it and then wiping or centrifuging to remove the excess coating to obtain a uniform coating on the surface of the device. (col. 16, lines 26-45). In contrast to PACETTI, SHEU describes a surface treatment to create an ionic polymeric layer that includes the use of plasma discharge or acid/base chemical modification, or adding the ionic or ionizable groups into the bulk material of the polymer (col. 6, lines 30- 35). None of these methods are used with PACETTI and no surface treatments are used in the present invention.

Third, in teaching that the "ionically bonded" hydrophilic coatings described in SHEU are durable (e.g., resistant to changes in pH, elevated temperatures, exposure to detergents or organic solvents, abrasion, repeated ultrasonic washings, etc.), SHEU

teaches away from the *biodisintegrable* polyelectrolyte multilayer coating regions claimed in presently pending Claims 4, 12, 13, 15-17, 20, 30 and 40.

Fourth, PACETTI uses solvent systems wherein the amount of solvent is in the range of 59.9-99.8% for the active ingredient coating (col. 8, line 63 – col. 9, line 5). Alternatively, thermoplastic polymers may be used for the primer with heat treating to evaporate the solvent (col. 16, lines 46-64). This approach is in contrast to the technology described in SHEU. Although SHEU mentions dip-coating for use with a substrate having an anionic polymer layer by dipping it into a polycationic solution, the concentration of the solution cannot exceed 5% (col.7, lines 55-58) at the peril of resulting in non-uniform coatings and increased drying times. The methods of PACETTI can tolerate polymer concentrations as high as 35% (col. 8, line 64- col.9, line 5). Thus, the combination of PACETTI and SHEU again fails.

Furthermore, as noted in a previous response, there is no reason why one of ordinary skill in the art would make the articles of PACETTI more hydrophilic, including SHEU's use of hydrogels. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007).

Accordingly, to arrive at the subject matter presently claimed would require, at the very least, undue and impermissible hindsight. See, for example, *Akzo N. V.* v. *U.S. International Trade Commission,* 808 F.2d 1241, 1480-81, 1 USPQ2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987), *Loctite Corp.* v. *Ultraseal Ltd.,* 781 F.2d 861, 874, 228 USPQ 90-99 (Fed. Cir. 1985). See also MPEP 2142, second paragraph.

If the device of PACETTI were modified in accordance with the teachings of SHEU, this would require the creation of an ionic polymeric layer over the diffusion barrier layer of PACETTI, and a disordered polyelectrolyte coating ionically bound to the ionic polymeric layer, which modification would result in the creation of a durable hydrophilic coating (e.g., resistant to changes in pH, elevated temperatures, exposure to detergents or organic solvents, abrasion, repeated ultrasonic washings, etc.) and would be expected to interfere with, or even prevent, the controlled release of active agent as sought by PACETTI. See *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Thus, while the combination of SHEU with PANCETTI is not taught or suggested, even if one were able to combine PANCETTI with SHEU, the likely result would be a medical device with better wettability on the surface but with (a) an inability to retain the

functionality of PACETTI's layer to control the rate of drug diffusion and (b) the likelihood that the methods used to make the coatings of SHEU would not be useful in modifying the devices of PACETTI. Thus there would be no reasonable expectation of success associated with the modification being proposed by the Examiner.

For the reasons described above, reconsideration and withdrawal of the rejection of Claims 1, 4-7, 9-10, 20-30, 33-34 and 37-41 under 35 U.S.C. 103 are requested.

Rejection Under 35 U.S.C. §103(a) Over PACETTI in View of SHEU and AMON

The Examiner has rejected Claims 12, 13 and 15-19 under 35 U.S.C. §103(a) on the basis of PACETTI in view of SHEU and further in view of Amon et al (US Patent 5,735,896) ("AMON"). This rejection is respectfully traversed for the reasons described above for PACETTI and SHEU and further for the reasons described herein.

The Examiner agrees that PACETTI does not disclose a stent made of a ceramic surface. The Examiner relies on AMON to provide a teaching of a stent made of metal or ceramic. This rejection is not supportable under the standards cited above. The technology of AMON is completely different than either the technologies of PACETTI or SHEU.

AMON uses semiconductor technology to create an extra strong adherence between an implanted prosthesis and a biocompatible coating. There is no inclusion of a therapeutic agent, and there is no description of any surface depression or pore or any layer placed over a therapeutic agent requiring control of its diffusion rate. AMON uses surface treatment (Abstract), again taking out it of the boundaries of PACETTI and going even further in the direction of surface treatment than SHEU. In fact, manufacturing techniques for AMON use an intense form of surface treatment and cathodic vapor deposition. Coating temperatures are required to be kept constant at around 250 degrees C (col. 2, lines 51-54). Such temperatures are not taught as acceptable for PACETTI and the technology is completely different than SHEU. Also, there is no reason to combine these references as some of the teachings in the individual references are in conflict and any combination would be achieved only by using hindsight reconstruction.

Even if the references were combined, it would still not achieve the present invention. There is no layer with particles as a diffusion modulating layer required by

PACETTI and certainly no hydrophilic layers as required by SHEU. Any combination of these references would not result in the claimed invention which is:

> A medical article comprising: (a) a ceramic or metallic region whose surface comprises a plurality of depressions; (b) a multilayer coating region comprising multiple polyelectrolyte layers deposited over said surface wherein each polyelectrolyte layer has a net charge opposite in sign from the adjacent layers; and (c) a therapeutic agent disposed within the depressions beneath said multilayer coating region, wherein the multilayer coating region extends over the therapeutic-agent-containing surface depressions to provide enclosed cavities which are occupied by the therapeutic agent.

For the reasons described above, reconsideration and withdrawal of the rejection of Claims 12, 13 and 15-19 under 35 U.S.C. §103 are requested.

Rejection Under 35 U.S.C. §103(a) Over PACETTI in View of SHEU and ANDERSON

The Examiner has rejected Claim 31 under 35 U.S.C. §103(a) on the basis of PACETTI in view of SHEU and further in view of Anderson et al (US Application Publication Number 2005/0172852) ("ANDERSON"). This rejection is respectfully traversed for the reasons described above for PACETTI and SHEU and further for the reasons described herein.

ANDERSON is a reference directed to tattoos. This reference describes technology useful for tissue marking, especially in the art of tattoos. The citation of ANDERSON as a bare disclosure of a metal oxide with a porous surface is not understood and certainly not supportable. The Examiner refers to paragraph 29 of ANDERSON as disclosing coating a metal oxide in order to have a porous surface. The text of paragraph 29, however, refers to forming a coating, a variable appearance material or an absorption component or mixtures thereof which will absorb electromagnetic radiation. The word "porous" does not even appear in this paragraph. In the previous Response, the Examiner was requested for a more extensive explanation of ANDERSON's relevance to the invention and the ability to combine a tattoo reference with a medical device reference. The Examiner has not done this.

For the reasons described above, reconsideration and withdrawal of the rejection of Claim 31 under 35 U.S.C. §103 are requested.

Rejection Under 35 U.S.C. §103(a) Over HARISH in View of SHEU

The Examiner has rejected Claim 35 under 35 U.S.C. §103(a) on the basis of Harish et al (US Patent 6,506,437) ("HARISH") in view of SHEU. This rejection is respectfully traversed based on the deficiencies described above for SHEU and further for the reasons described herein.

HARISH discloses a method for coating medical devices having a plurality of "depots" where the depots are filled with a mixture of therapeutic agent and polymer filling the depots. HARISH discloses that when there is a polymeric topcoat, the particulars of the topcoat also control release (col. 10, line 65 - col. 11, line 9).

The Examiner has agreed that HARISH does not disclose "polyelectrolyte layers covering a stent. The Examiner then tries to rely on SHEU but, as has previously been explained, SHEU does not teach or suggest that any therapeutic agents are released from the polyelectrolyte coating. It has also been noted above that SHEU does not teach or suggest that the polyelectrolyte coating is useful to control the release of any bioactive agents. Rather, SHEU discloses medical articles, including contact lenses, having polyelectrolyte coatings for the purpose of rendering them hydrophilic.

Furthermore, if the device of HARISH were modified in accordance with the teachings of SHEU, this would result in the creation of an ionic polymeric layer and a disordered polyelectrolyte coating, which structure is noted in SHEU to be very stable, and which would interfere with, or even prevent, the controlled release of active agent as taught by HARISH.

With respect to the *method* aspects of Claim 35, this claim requires a method that comprises:

> (a) inserting a disintegrable material into said depressions to form filled depressions, (b) depositing polyelectrolyte layers over the filled depressions by a method comprising depositing a first polyelectrolyte layer having a first net charge over the substrate, depositing a second polyelectrolyte layer having a second net charge that is opposite in sign to the first net charge over the first polyelectrolyte layer, and depositing additional polyelectrolyte layers, each having a net charge that is opposite in sign to the preceding layer, (c) subsequently removing the disintegrable material from the depressions and (d) subsequently introducing said therapeutic agent into the depressions.

Thus, after the polyelectrolyte layer is applied in step (b), the disintegrable material that was placed in the depressions in step (a) is removed in step (c). Only then is the agent added to the depressions in step (d). No method of this nature is taught or suggested in HARISH and/or SHEU.

For the above reasons, reconsideration and withdrawal of the rejection of Claim 35 under 35 U.S.C. §103 are respectfully requested.

CONCLUSION

Applicants submit that Claims 1, 4-7, 9-13, 15-31, 33-35 and 37-41 are in condition for allowance, early notification of which is earnestly solicited. It is believed that this Response is being submitted in time for an Advisory Action should the Examiner require further changes to the Claims. Should the Examiner be of the view that an interview would expedite consideration of this Response or of the application at large, the Examiner is requested to telephone the Applicant's attorney at the number listed below in order to resolve any outstanding issues in this case.

Respectfully submitted,

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Date: July 9, 2009